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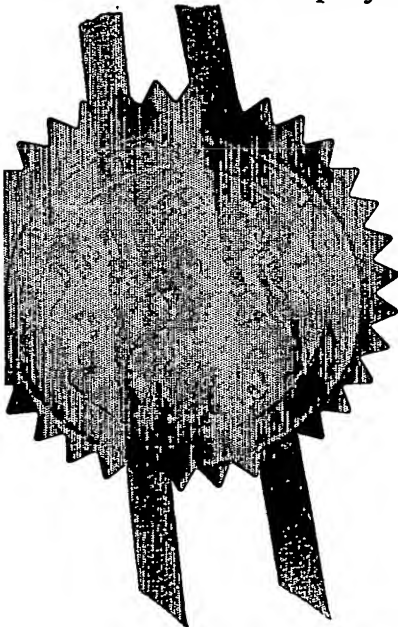
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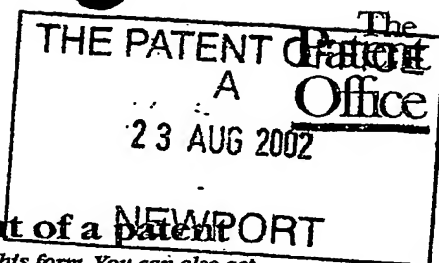
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1/77

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1. Your reference

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2. Patent application number

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0219660.8

23 AUG 2002

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01/7700 0.00-0219660.8

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number (if you know it)

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC USE

5. Name of your agent (if you have one)

Lucy Clare Padget

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number (if you know it)

8340762001

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Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

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Continuation sheets of this form

Description 8

Claim(s) 2

Abstract 1

Drawing(s)

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Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
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11. I/We request the grant of a patent on the basis of this application.

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Date

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22/08/2002

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Jennifer C Bennett - 01625 230148

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THERAPEUTIC USE

The present application refers to *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, hereafter "Compound (I)", and its use in the treatment of cancer in a warm blooded animal such as man. The invention also relates to the use of pharmaceutical compositions containing Compound (I), or a pharmaceutically acceptable salt thereof, in a method of treating cancer in a warm blooded animal such as man, and to the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of medicament for use in a method of treating cancer in a warm blooded animal such as man.

Cancer affects an estimated 10 million people worldwide. This figure includes incidence, prevalence and mortality. More than 4.4 million cancer cases are reported from Asia, including 2.5 million cases from Eastern Asia, which has the highest rate of incidence in the world. By comparison, Europe has 2.8 million cases, North America 1.4 million cases, and Africa 627,000 cases.

In the UK and US, for example, more than one in three people will develop cancer at some point in their life. Cancer mortality in the U.S. is estimated to account for about 600,000 a year, about one in every four deaths, second only to heart disease in percent of all deaths, and second to accidents as a cause of death of children 1-14 years of age. The estimated cancer incidence in the U.S. is now about 1,380,000 new cases annually, exclusive of about 900,000 cases of non-melanotic (basal and squamous cell) skin cancer.

Cancer is also a major cause of morbidity in the UK with nearly 260,000 new cases (excluding non-melanoma skin cancer) registered in 1997. Cancer is a disease that affects mainly older people, with 65% of cases occurring in those over 65. Since the average life expectancy in the UK has almost doubled since the mid nineteenth century, the population at risk of cancer has grown. Death rates from other causes of death, such as heart disease, have fallen in recent years while deaths from cancer have remained relatively stable. The result is that 1 in 3 people will be diagnosed with cancer during their lifetime and 1 in 4 people will die from cancer. In people under the age of 75, deaths from cancer outnumber deaths from diseases of the circulatory system, including ischaemic heart disease and stroke. In 2000, there were 151,200 deaths from cancer. Over one fifth (22 per cent) of these were from lung cancer, and a quarter (26 per cent) from cancers of the large bowel, breast and prostate.

Worldwide, the incidence and mortality rates of certain types of cancer (of stomach, breast, prostate, skin, and so on) have wide geographical differences which are attributed to racial, cultural, and especially environmental influences. There are over 200 different types of cancer but the four major types, lung, breast, prostate and colorectal, account for over half of all cases diagnosed in the UK and US. Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.

Current options for treating cancers include surgical resection, external beam radiation therapy and / or systemic chemotherapy. These are partially successful in some forms of cancer, but are not successful in others. There is a clear need for new therapeutic treatments.

Recently, endothelin A receptor antagonists have been identified as potentially of value in the treatment of cancer. (Cancer Research, 56, 663-668, February 15th, 1996 and Nature Medicine, Volume 1, Number 9, September 1999, 944-949).

The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp²¹-Val²² bond of their corresponding proendothelins by an endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known and have a characteristic long duration of action. They exhibit a wide range of other activities including cell proliferation and mitogenesis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents.

The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including cancers.

The present invention concerns the surprising finding that Compound (I) is a particularly potent anti-cancer agent. Compound (I) is described as an endothelin receptor antagonist in WO96/40681, and although in WO96/40681 it is acknowledged that elevated endothelin levels have been found in a number of disease states in man including certain cancers, there is no hint or suggestion that this compound would possess the particular beneficial efficacious, metabolic and toxicological profiles that makes it such a potent anti-cancer agent. In fact, the present inventors have surprisingly established that Compound (I) is a

specific endothelin-A (ET_A) antagonist and has no measurable activity against endothelin-B (ET_B).

The ET_A receptor has been shown, via a variety of mechanisms, to be the more important pathological receptor of the two identified endothelin receptors in oncology: in the reduction of abnormal cell proliferation (Bagnato et. al., (1995), Clin Cancer Res 1, 1059-1066); as a anti-apoptotic (Wu Wang et. al., (1997), Biochem J., 328, 733-737); as an anti-angiogenic agent (Spinella et al., (2002), J. Biol. Chem, 227(31), 27850-27855); and as an inhibitor of bone metastases (Guise et. al., ASCO (2000) abstract 331 and Nelson, et. al., (1999), Urology 53, 1063-1069) in addition to mediating pain which is a common co-morbidity in cancer. It has been shown (Dahlof et al., (1990), J Hypertens, 8, 811- 817) that large doses of endothelin-1 causes pain, but that this can be inhibited by an ET_A antagonist (e.g. Davar et al., (1998), Neuroreport 9, 2279-2283 and De Mello et al., (1998), Pain, 77, 261-269). Therefore in another aspect of the invention, Compound (I) is administered for the prevention or treatment of pain mediated by the endothelin system, in particular that associated with elevated endothelin-1 levels.

Conversely, there is emerging evidence (e.g. Cattaruzza et. al., (2002), FASEB J. 14(7), 991-998 and Okazawa et. al., (1998), J Biol Chem, 273, 12581-12592) that the ET_B receptor is involved in apoptotic signalling. The blocking of pro-apoptotic pathways would be undesirable in the treatment of cancer, hence a compound that specifically targeted the ET_A receptor while leaving the ET_B receptor unaffected would be of the greatest utility in the treatment of cancer. Compound (I) is such a compound.

Compound (I) by acting specifically on the ET_A receptor has many advantages over endothelin antagonists that also have measurable ET_B activity. For instance Compound (I) could be administered to a patient without the administrator or prescribing medical practitioner needing to titrate the dose of Compound (I) looking for signs of ET_B activity (for example rhinitis and oedema). Furthermore, larger doses could potentially be administered because there would be no ET_B side effects.

Therefore according to the present invention, there is provided Compound (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a warm blooded animal such as man.

According to another feature of the present invention, there is provided Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer in a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of treating cancer which comprises administering an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a
5 pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the reduction of abnormal proliferation in a
10 cancerous cell or inducing differentiation of a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the reduction of abnormal proliferation in a cancerous cell or inducing differentiation of a
15 cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided a method for reducing abnormal proliferation in a cancerous cell or inducing differentiation of a cancerous cell which comprises administering an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

20 According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the reduction of abnormal proliferation in a cancerous cell or inducing differentiation of a cancerous cell in a warm blooded animal such as man.

25 In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in inducing apoptosis in a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in
30 inducing apoptosis in a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided a method of inducing apoptosis in a cancerous cell which comprises administering an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in inducing apoptosis in a cancerous cell in a warm blooded animal such as man.

5 In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, as an anti-angiogenic and vascular targeting agent in blood vessels supplying a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an
10 anti-angiogenic and vascular targeting agent in blood vessels a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided a method of providing an anti-angiogenic and vascular targeting agent in blood vessels supplying a cancerous cell which comprises administering an effective amount of Compound (I), or a pharmaceutically
15 acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use as an anti-angiogenic and vascular targeting agent in blood vessels a cancerous cell in a
20 warm blooded animal such as man.

By the term "vascular targeting agent" it is to be understood that the site of action of Compound (I) would be on the vasculature itself rather than the tumour.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, as an inhibitor of bone metastases and an inhibitor of
25 invasion in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an inhibitor of bone metastases and an inhibitor of invasion in a warm blooded animal such as man.

30 In another aspect of the invention there is provided a method of inhibiting bone metastases and inhibiting invasion which comprises administering an effective amount of Compound (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use as an inhibitor of bone metastases and an inhibitor of invasion in a warm blooded animal
5 such as man.

In another aspect of the invention there is provided the use of Compound (I), or a pharmaceutically acceptable salt thereof, in the prevention or treatment of pain associated with elevated endothelin-1 production in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of Compound (I), or a
10 pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the prevention or treatment of pain associated with elevated endothelin-1 production in a warm blooded animal such as man.

In another aspect of the invention there is provided a method of treating pain associated with elevated endothelin-1 production which comprises administering an effective
15 amount of Compound (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for
20 use in the prevention or treatment of pain associated with elevated endothelin-1 production in a warm blooded animal such as man.

Where cancer is referred to, particularly it refers to oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, kaposi sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma,
25 lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, renal cancer, lymphoma and leukaemia. More particularly it refers to prostate cancer. In addition, more particularly it refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and / or breast cancer. Furthermore, more particularly it refers to bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal
30 cancer. In another embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces metastases to the bone. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces skin metastases.

Where pain is referred to, this is pain associated with raised endothelin-1 levels. Particularly this pain associated with cancer. More particularly it is pain associated with prostate cancer.

Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid.

Endothelin human receptor binding assay

Human recombinant ET_A or ET_B receptors were expressed in mouse erythroleukaemic (MEL) cells and membranes prepared for competition binding studies using ^{125}I -labelled ET-1 as the radioligand. Incubations were carried out in triplicate in the presence of Compound (I), 10^{-10} - 10^{-4} M in half log increments, and inhibition of ET-1 binding was expressed as a geometric mean pIC_{50} value with 95% confidence limits.

Results

The pIC_{50} (negative log of the concentration of compound required to displace 50% of the ligand) for Compound (I) at the ET_A receptor was 8.27 [8.23 - 8.32] ($n=4$). Displacement curves were normal with slopes close to unity. Compound (I) had no measurable affinity for the ET_B receptor with a mean displacement of $1.2 \pm 0.7\%$ ($n=3$) at a concentration of $10^{-4}M$, a figure well within the limits of sensitivity of the assay.

Conclusion

Compound (I) is a high affinity ligand for the human ET_A receptor and is ET_A specific, having no significant ET_B receptor affinity.

In a further embodiment of the present invention Compound (I), or a pharmaceutically acceptable salt thereof, is administered to a cell or individual prior to the development of cancer. For example, a person at risk of developing cancer may be treated with Compound (I), or a pharmaceutically acceptable salt thereof, to prevent or inhibit the development of cancer and/or to prevent the development of metastases.

Compound (I), or a pharmaceutically acceptable salt thereof, can be administered for therapeutic or prophylactic use to a warm blooded animal such as man by methods known in

the art. Administration can occur directly at the tumour site, or particularly, systemic administration.

Compound (I), or a pharmaceutically acceptable salt thereof, can be administered for therapeutic or prophylactic use to a warm blooded animal such as man in the form of conventional pharmaceutical compositions. The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of Compound (I), or a pharmaceutically acceptable salt thereof, administered would be that sufficient to provide the desired pharmaceutical effect. For instance, Compound (I) could be administered to a warm-blooded animal orally, at a unit dose less than 1g daily.

Claims

1. The use of *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, in the
5 manufacture of a medicament for use in the treatment of cancer in a warm blooded animal such as man.
2. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the reduction of abnormal proliferation
10 in a cancerous cell or inducing differentiation of a cancerous cell in a warm blooded animal such as man.
3. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inducing apoptosis in a cancerous cell
15 in a warm blooded animal such as man.
4. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an anti-angiogenic and vascular targeting agent in blood vessels a cancerous cell in a warm blooded animal such as man.
20
5. The use according to any one of claims 1-4 wherein the cancer is oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, kaposi sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung
25 cancer(SCLC), gastric cancer, head and neck cancer, renal cancer lymphoma and leukaemia.
6. The use according to any one of claims 1-4 wherein the cancer is prostate cancer.
7. The use according to any one of claims 1-4 wherein the cancer is SCLC, NSCLC,
30 colorectal cancer, ovarian cancer and / or breast cancer.
8. The use according to any one of claims 1-4 wherein the cancer is bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal cancer.

9. The use or method according to any one of claims 1-4 wherein the cancer is in a metastatic state.

10. The use according to any one of claims 1-9 wherein the cancer is producing bone
5 metastases.

11. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an inhibitor of bone metastases and an inhibitor of invasion in a warm blooded animal such as man.

10

12. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the prevention or treatment of pain associated with elevated endothelin-1 production in a warm blooded animal such as man.

A B S T R A C T

5

TITLE : THERAPEUTIC USE

The use of *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, in the treatment of cancer in a warm blooded animal such as man is described.

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